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Identifying common genetic variants in blood pressure due to polygenic pleiotropy with associated phenotypes

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Abstract

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Authors' contributions

Andreassen and Dale designed study; Djurovic, Schork, Reppe collected data, Schork prepared data; Dale performed the statistical analysis with assistance from Thompson, Wang, Zuber, Reppe; Andreassen and McEvoy drafted manuscript; Gautvik, Karlsen, Aukrust, Barrett-Connor, Desikan, McEvoy, Dale, Andreassen interpreted data; all authors critically revised manuscript and approved final version.

Disclosures

None reported.

Blood pressure is a critical determinant of cardiovascular morbidity and mortality. It is affected by environmental factors, but has a strong heritable component. Despite recent large genome-wide association studies, few genetic risk factors for blood pressure have been identified. Epidemiological studies suggest associations between blood pressure and several diseases and traits, which may partly arise from a shared genetic basis (genetic pleiotropy). Using genome-wide association studies summary statistics and a genetic pleiotropy-informed conditional False Discovery Rate method, we systematically investigated genetic overlap between systolic blood pressure and 12 co-morbid traits and diseases. We found significant 'enrichment' of single nucleotide polymorphisms associated with systolic blood pressure as a function of their association with body mass index, low density lipoprotein, waist hip ratio, schizophrenia, bone mineral density, type 1 diabetes and celiac disease. In contrast, the magnitude of enrichment due to shared polygenic effects was smaller with the other phenotypes (triglycerides, high density lipoproteins, type 2 diabetes, rheumatoid arthritis, and height). Applying the conditional False Discovery Rate method to the enriched phenotypes, we identified 62 loci associated with systolic blood pressure (False Discovery Rate < 0.01), including 42 novel loci. The observed polygenic overlap between systolic blood pressure and several related disorders indicates that the epidemiological associations are not mediated solely via lifestyle factors, but also reflect an etiological relation that warrants further investigation. The new gene loci identified implicate novel genetic mechanisms related to lipid biology and the immune system in systolic blood pressure.

Keywords

Genome-wide association study; genetic pleiotropy; systolic blood pressure; comorbid disorders

INTRODUCTION

High blood pressure affects over one billion individuals¹, and even small increments increase morbidity and mortality. Though heritability estimates of systolic blood pressure (SBP) exceed 50%^{2,3}, genes identified to date explain only a small proportion of heritability⁴. It has been argued that the genetic architecture of blood pressure regulation in the general population cannot be explained by commonly occurring genetic variation, suggesting that genome-wide association studies (GWAS) will continue to fail in hypertension^{5,6}. However, recent results indicate that GWAS have the potential to explain a greater proportion of the heritability of most common complex phenotypes^{7,8}. This polygenic architecture suggests that a large number of Single Nucleotide Polymorphisms (SNPs) will have associations too weak to be identified using traditionally employed analytic methods and limited sample sizes⁹. This has led to recent National Institute of Health and European Union calls for new cost-effective analytical methods to reliably identify a larger proportion of SNPs associated with complex diseases and traits using existing GWAS since recruitment and genotyping of new participants are expensive. One such approach relies on genetic pleiotropy¹⁰, i.e. the association of individual SNPs or genes with two or more phenotypes. Given the large number of traits in humans, and the relatively small number of genes, some genes are likely to affect multiple traits. Moreover, since there are often overlapping traits among behaviorally or clinically defined phenotypes, shared genetic influences between such phenotypes are likely.

Epidemiological studies have identified several major risk factors for cardiovascular disease (CVD)^{11,12} including hypertension, obesity, diabetes and dyslipidemia^{1,13-15}. Several other traits and disorders have also been associated with blood pressure, including height^{2,3,16}, osteoporosis^{4,17}, schizophrenia^{5,6,18}, diabetes^{7,8,19}, and autoimmune disorders^{9,20}. However, observational and clinical studies cannot fully elucidate the etiologic relationship between

these phenotypes. Methods for assessing genetic pleiotropy offer great promise for delineating the basis of shared phenotypic correlations and for cost-effective identification of new loci^{10,21,22}. This could be particularly meaningful for ‘essential hypertension’, where multiple pathogenic processes are likely involved^{11,12,23}, and overlapping genetic associations with multiple phenotypes may be frequent. Here, we applied a recently developed genetic pleiotropy-informed analytical method for GWAS that captures more of the polygenic effects in complex disorders and traits (hereafter referred to as polygenic pleiotropy)²². We used this approach to leverage the power of multiple large independent GWAS for identifying SNPs exhibiting pleiotropy between SBP and 12 associated traits and disorders where recent GWAS results are available: bone mineral density (BMD)²⁴, low density lipoprotein (LDL) cholesterol, high density lipoprotein (HDL) cholesterol, triglycerides (TG)²⁵, type 2 diabetes (T2D)²⁶, body mass index (BMI)²⁷, waist to hip ratio (WHR)²⁸, height (HT)²⁹, schizophrenia (SCZ)³⁰, type 1 diabetes (T1D)³¹, Rheumatoid Arthritis (RA)³² and Celiac Disease (CeD)^{33,34}. By combining data from these different GWAS, we hypothesized that the genetic pleiotropy-informed approach can improve discovery of SBP genes, and inform the etiologic relationship between blood pressure and epidemiologically related phenotypes.

METHODS

Participant Samples

We obtained complete GWAS results in the form of summary statistics p-values from public access websites or through collaboration with investigators (Table 1). Details on the inclusion criteria and phenotype characteristics of the different GWAS are described in the original publications^{4,25-28}. There was some overlap among several of the participants in the CVD risk factor GWAS and the SBP GWAS sample⁴. The relevant institutional review boards or ethics committees approved the research protocol of the individual GWAS and all participants gave written informed consent. All studies adhered to the principles of the Declaration of Helsinki.

Statistical Analyses

Genomic Control—We applied a control method using only intergenic SNPs to compute the inflation factor, λ_{GC} and divided all test statistics by λ_{GC} , as detailed in prior publications^{21,22}.

Conditional Quantile-Quantile (Q-Q) plots for pleiotropic enrichment—

Enrichment of statistical association relative to that expected under the global null hypothesis can be visualized through Q-Q plots of nominal p-values obtained from GWAS summary statistics. Genetic enrichment results in a leftward shift in the Q-Q curve, corresponding to a larger fraction of SNPs with nominal $-\log_{10}$ p-value greater than or equal to a given threshold. *Conditional* Q-Q plots are constructed by creating subsets of SNPs based on the significance of each SNP's association with a related phenotype, and computing Q-Q plots separately for each level of association (for further details, see references 21, 22). We constructed conditional Q-Q plots of empirical quantiles of nominal $-\log_{10}(p)$ values for SNP association with SBP for all SNPs, and for subsets of SNPs determined by the nominal p-values of their association with each of the 12 related phenotypes ($-\log_{10}(p) = 0, -\log_{10}(p) = 1, -\log_{10}(p) = 2$, and $-\log_{10}(p) = 3$ corresponding to $p = 1, p = 0.1, p = 0.01$, and $p = 0.001$, respectively). The nominal p-values ($-\log_{10}(p)$) are plotted on the y-axis, and the empirical quantiles ($-\log_{10}(q)$, where $q=1-\text{cdf}(p)$) are plotted on the x-axis. To assess polygenic effects, we focused the conditional Q-Q plots on SNPs with nominal $-\log_{10}(p) < 7.3$ (corresponding to $p > 5 \times 10^{-8}$).

Conditional False Discovery Rate (FDR)—Enrichment seen in the conditional Q-Q plots can be directly interpreted in terms of False Discovery Rate (FDR)^{21,22} (equivalent to $1 - \text{True Discovery Rate (TDR)}^{35}$). We applied a conditional FDR method^{22,36,37}, and constructed TDR plots, as described earlier^{21,22}, and detailed in Online Supplement (please see <http://hyper.ahajournals.org>).

Conditional statistics – test of association with Systolic Blood Pressure—To improve detection of SNPs associated with SBP, we conditioned SNPs based on p-values in the related phenotype^{21,22}. We then assigned a conditional FDR value (denoted as $\text{FDR}_{\text{SBP} | \text{related-phenotype}}$) for SBP to each SNP, for each related phenotype by interpolation, using a two-dimensional look-up table of conditional FDR values^{21,22} computed for each of the specific datasets used in the current study (Figure S3, please see <http://hyper.ahajournals.org>). All SNPs with $\text{FDR}_{\text{SBP} | \text{related-phenotype}} < 0.01$ ($-\log_{10}(\text{FDR}_{\text{SBP} | \text{related-phenotype}}) > 2$) in SBP given association with any of the 12 related phenotypes are listed in Table 1 after ‘pruning’ (i.e., removing all SNPs with $r^2 > 0.2$ based on 1000 Genomes Project linkage disequilibrium (LD) structure). A significance threshold of $\text{FDR} < 0.01$ corresponds to 1 false positive per 100 reported associations.

Conditional FDR Manhattan plots—To illustrate the localization of the genetic markers associated with SBP given the related phenotype effect, we used a ‘Conditional FDR Manhattan plot’, plotting all SNPs within an LD block in relation to their chromosomal locations. The strongest signal in each LD block was identified by ranking all SNPs in increasing order, based on the conditional FDR value for SBP, and then removing SNPs in $\text{LD } r^2 > 0.2$ with any higher ranked SNP. Thus, the selected locus was the most significantly associated with SBP in each LD block.

RESULTS

Pleiotropic enrichment – polygenic overlap

Conditional Q-Q plots for SBP conditioned on nominal p-values of association with LDL, BMI, BMD, T1D, SCZ, and CeD showed enrichment across different levels of significance (Figure 1A-F). For LDL, the proportion of SNPs in the $-\log_{10}(p_{\text{LDL}}) \geq 3$ category reaching a given significance level (e.g., $-\log_{10}(p_{\text{SBP}}) > 6$) was roughly 100 times greater than for $-\log_{10}(p_{\text{LDL}}) = 0$ category (all SNPs), indicating a very high level of enrichment (Figure 1A). A similar level of enrichment was seen for BMI and SCZ (Figure 1B,C); CeD, T1D and BMD also showed a high level of enrichment (Figure 1D-F). Weaker pleiotropic enrichment was seen for WHR (Figure S1, please see <http://hyper.ahajournals.org>), with little or no evidence for enrichment in RA, HDL, TG, T2D, HT (Figure S1, please see <http://hyper.ahajournals.org>). We also illustrate the high level of polygenic pleiotropic enrichment in LDL, BMI, BMD, T1D, SCZ, and CeD using ‘Enrichment Plots’ (Figure S2, please see <http://hyper.ahajournals.org>).

Gene loci associated with SBP

The “conditional FDR” Manhattan plot in Figure 2 shows the 62 independent gene loci significantly associated with SBP based on conditional $\text{FDR} < 0.01$ obtained from associated phenotypes. The 30 complex loci and 32 single gene loci (after pruning) were located on 16 chromosomes (Table 2). Only 11 of these loci would have been discovered using standard statistical methods (Bonferroni correction; bold values in the “SBP p-value” column, Table 2). Using the FDR method, 25 loci were identified (bold values in the “SBP-FDR” column, Table 2). The remaining 37 loci would not have been identified in the current sample without using the pleiotropy-informed conditional FDR method. Of the 62 loci identified, 42 were novel; 20 were reported in the primary analysis of the current sample⁴.

Many of these new loci are located in regions with borderline significant association with SBP in previous studies⁴. Of interest, several loci had multiple pleiotropic SNPs from several associated phenotypes, indicating overlapping genetic factors among these phenotypes.

Follow-up Ingenuity Pathways Analysis (IPA) are presented in Table S3 and S4 (please see <http://hyper.ahajournals.org>) identifying the traits in the categories “Cardiovascular disease” or “Cardiovascular System Development and Function”, respectively, that may be affected by the gene heterogeneities in the vicinity of the indicated SBP associated genes. Figure S4, made by the network function in IPA, demonstrates that a large proportion of SBP associated genes are functionally related (please see <http://hyper.ahajournals.org>).

DISCUSSION

Our findings demonstrate polygenic pleiotropy between SBP and BMI, T1D, SCZ, CeD and BMD, with strongest pleiotropy between SBP and LDL. Combining GWAS data from multiple different phenotypes, we identify 62 SBP susceptibility loci, including 42 novel loci.

In the original SBP GWAS sample, 29 loci were identified⁴. By combining the original SBP sample with GWAS of epidemiologically related phenotypes, we found significant pleiotropic signals in 62 loci. Thus, even though the original SBP GWAS was quite large⁴, the increased power provided by additional GWAS of associated phenotypes together with the FDR method more than doubled gene discovery. These findings underline the cost-effectiveness of the current statistical methods, and strongly suggest that SBP is a highly polygenic trait, in line with recent findings³⁸.

Our findings also provide novel insights into the relationship between SBP and other major CVD risk factors, which frequently co-occur. The combination of dyslipidemia (primarily increased TG levels and decreased HDL levels), T2D, and high blood pressure forms the metabolic syndrome¹²⁻¹⁶. These results demonstrate an interesting genetic dissociation among cardiovascular risk factors. We found that LDL, a classic CVD risk factor, showed strongest pleiotropy with SBP while factors associated with the metabolic syndrome (TG, HDL, and T2D) showed little genetic pleiotropy with SBP. Further research is needed to determine whether there is strong genetic pleiotropy among the metabolic risk factors that would provide a genetic basis for the metabolic syndrome. The strong pleiotropy between LDL and SBP suggests that many genes related to lipid biology are pleiotropic with SBP and suggests common mechanisms related to atherosclerosis. This is further supported by the individual loci identified, of which the majority was based on conditional FDR with LDL, BMI or WHR. Several of the genes in LD with these new SBP-associated loci are involved in lipid metabolism and regulation. Lipid metabolism regulation may also underlie the observed pleiotropy between SBP and BMD, as suggested by gene expression in bone tissue³⁹. However, age-related mechanisms may also underlie the overlap seen between SBP and BMD⁴⁰.

Pleiotropy is defined as a single gene or variant being associated with more than one distinct phenotype⁴¹. Rather than representing genetic pleiotropy, it is also possible that some of the loci identified in the current study may underlie common aspects of the SBP and CVD phenotypes. Moreover, the shared genetic loci may also represent mediated pleiotropy. For example, for LDL and SBP the overlap may be due to the fact that lipid deposition leads to stiff arteries and thus higher blood pressure.

Another novel finding is the overlap between SBP and immune-related disorders, including CeD and T1D. Based on conditional analysis of these two phenotypes, 24 loci were

identified. These phenotypes also showed strong polygenic pleiotropy, with clear enrichment in the Q-Q plots. While previous studies have suggested a link between T2D and SBP, the present study found an overlap between T1D, but not T2D, and SBP, suggesting immune-mediated rather than metabolic links between diabetes and SBP. The immune-related mechanisms that are involved in SBP seem to be quite specific as we found little enrichment with RA, a prototypical auto-immune disorder. Moreover, while we found no or weak association with other inflammatory bowel disorders (data not shown), CeD a T-cell mediated disease⁴², showed much stronger enrichment. SCZ also showed strong enrichment with 12 independent SBP loci identified based on enrichment from the SCZ GWAS. In a previous study²¹ we successfully used the polygenic pleiotropy approach to increase gene discovery in SCZ by enriching on CVD risk factors, identifying a shared genetic basis for the increased CVD mortality and higher incidence of hypertension in SCZ patients¹⁸. Our findings of several shared loci between SBP and SCZ point to common underlying mechanisms that warrant further experimental investigation.

Due to the overlap in some of the GWAS samples examined, we cannot exclude contribution from environmental or behavioral factors, or other non-genetic correlations. Still, our genetic pleiotropy results strongly imply the existence of shared pathophysiological processes across SBP and associated phenotypes because we controlled for pleiotropic inflation using genomic control correction of each primary single phenotype GWAS. Moreover, the overlapping loci are located on 16 chromosomes suggesting that the findings are not due to common genetic variation in potentially overlapping control groups. Further, the GWAS of blood lipids used the same sample to discover new genes for three different phenotypes²⁵. Since we do not have access to additional samples or individual sub-studies, we cannot provide evidence of replication, which is a limitation of the current study. However, we have previously shown that the genetic findings obtained using the conditional FDR approach employed here replicate at the same or higher rate than findings obtained with traditional GWAS methods. Importantly, we have also demonstrated that these FDR-based methods increase sensitivity for a given specificity thus improving statistical power for SNP detection²². Due to the overlap in some of the GWAS samples examined, we cannot exclude contribution from environmental or behavioral factors, or other non-genetic correlations.

Another limitation of the current study is our inability to relate the genetic findings to clinical outcomes, such as stroke and congestive heart failure, as we do not have access to clinical outcome measures. However the current findings suggest that leveraging more powerful statistical techniques, building on Empirical Bayesian mixture models, may be a fruitful approach to better select plausible candidate SNPs for improved polygenic risk scores⁴³ that may lead to personalized medicine approaches and potentially individual prediction of disease risk. We are currently working towards developing prediction and stratification algorithms that incorporate multiple small effects to increase prediction and classification power.

In conclusion, we found substantial genetic overlap between SBP and several related conditions, including BMI, WHR, T1D, SCZ, CeD, BMD and in particular LDL. This suggests an etiological relationship between these phenotypes that could include lipid disturbances and certain immunological pathways.

PERSPECTIVES

The current results demonstrate the feasibility of using a genetic epidemiology framework that leverages overlap in genetic signal from independent GWAS of associated phenotypes, both for cost-effective gene discovery and for elucidating the shared genetic basis between

related phenotypes. This approach identified 42 novel gene loci in SBP, arguing that GWAS have the potential to uncover more of the genetic basis of hypertension when new statistical methods are used. The observed polygenic overlap between SBP and several comorbid disorders indicates that the epidemiological associations are not mediated solely via lifestyle factors, but also reflect an etiological relation. Our findings also shed new light on the pathogenic mechanisms in SBP that warrants further investigation. The novel genetic loci identified here implicate genetic mechanisms related to lipid biology and the immune system in SBP. These findings may have implications for early diagnosis, prevention strategies and therapeutic regimens for hypertension.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Novelty and Significance

1. What Is New?

- We used new statistical methods to improve gene discovery
- We identified 42 novel gene loci associated with blood pressure
- We demonstrated shared genes between blood pressure and several associated diseases/traits

2. What Is Relevant?

- The new gene loci may inform the underlying genetic mechanisms of hypertension
- The genetic overlap with immune-mediated diseases and blood lipids suggests common mechanisms with hypertension
- The findings may have implications for early diagnosis, prevention strategies and therapeutic regimens in hypertension

3. Summary

We identified 42 new gene loci for blood pressure, and found genetic overlap between blood pressure and several associated diseases and traits, particularly immune-mediated diseases and blood lipids. This suggests an etiological relationship between hypertension and lipid disturbances and immunological abnormalities.

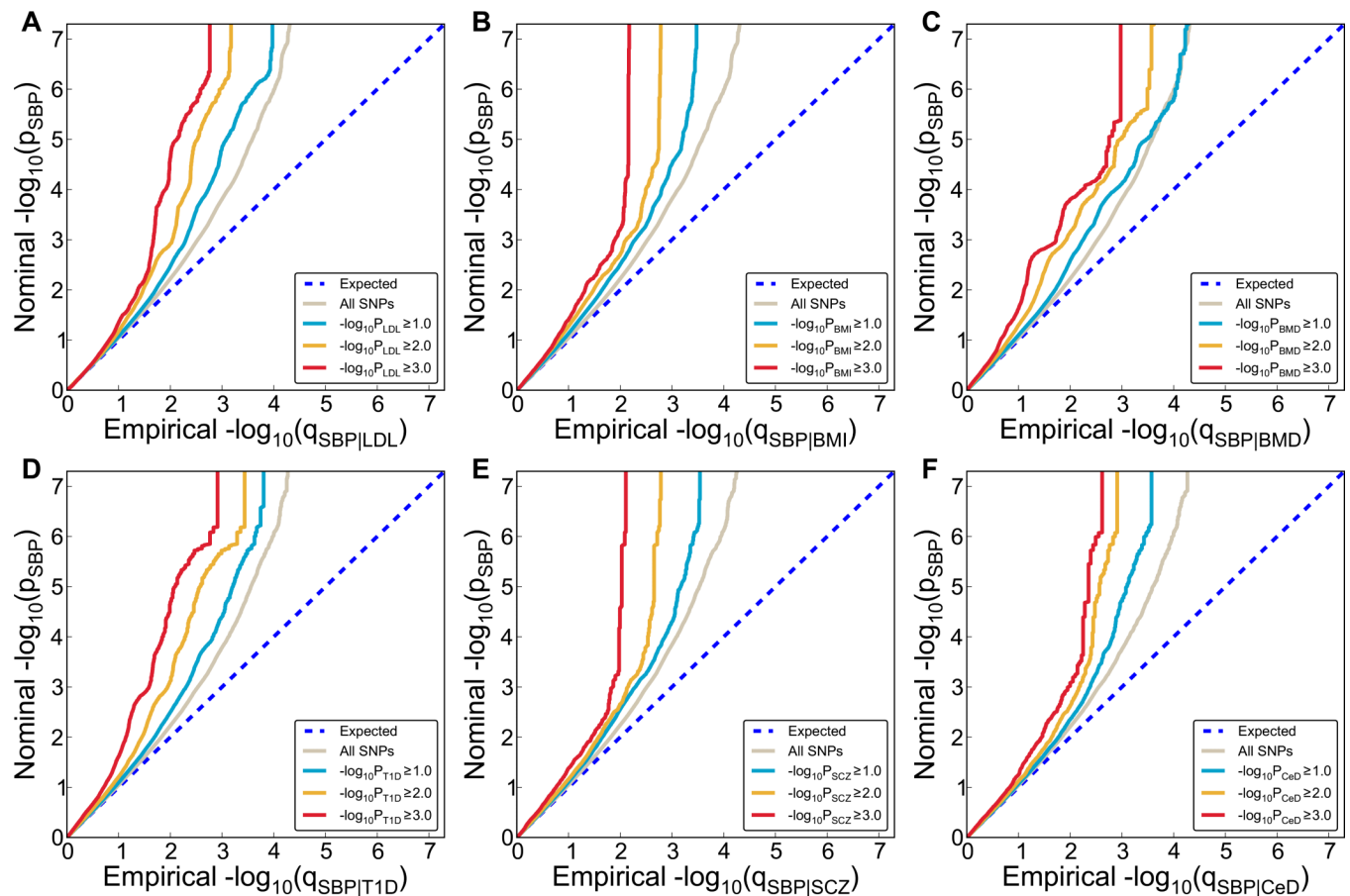


Figure 1. Q-Q plots of pleiotropic enrichment in SBP conditioned on associated phenotypes
Conditional Q-Q plot of nominal versus empirical $-\log_{10}$ p-values (corrected for inflation) in systolic blood pressure (SBP) below the standard GWAS threshold of $p < 5 \times 10^{-8}$ as a function of significance of association with **A)** Low density lipoprotein cholesterol (LDL), **B)** body mass index (BMI), **C)** bone mineral density (BMD), **D)** type 1 diabetes (T1D), **E)** schizophrenia (SCZ) and **F)** celiac disease (CeD) at the level of $-\log_{10}(p) > 0$, $-\log_{10}(p) > 1$, $-\log_{10}(p) > 2$, $-\log_{10}(p) > 3$ corresponding to $p < 1$, $p < 0.1$, $p < 0.01$, $p < 0.001$, respectively. Dotted lines indicate the null-hypothesis.

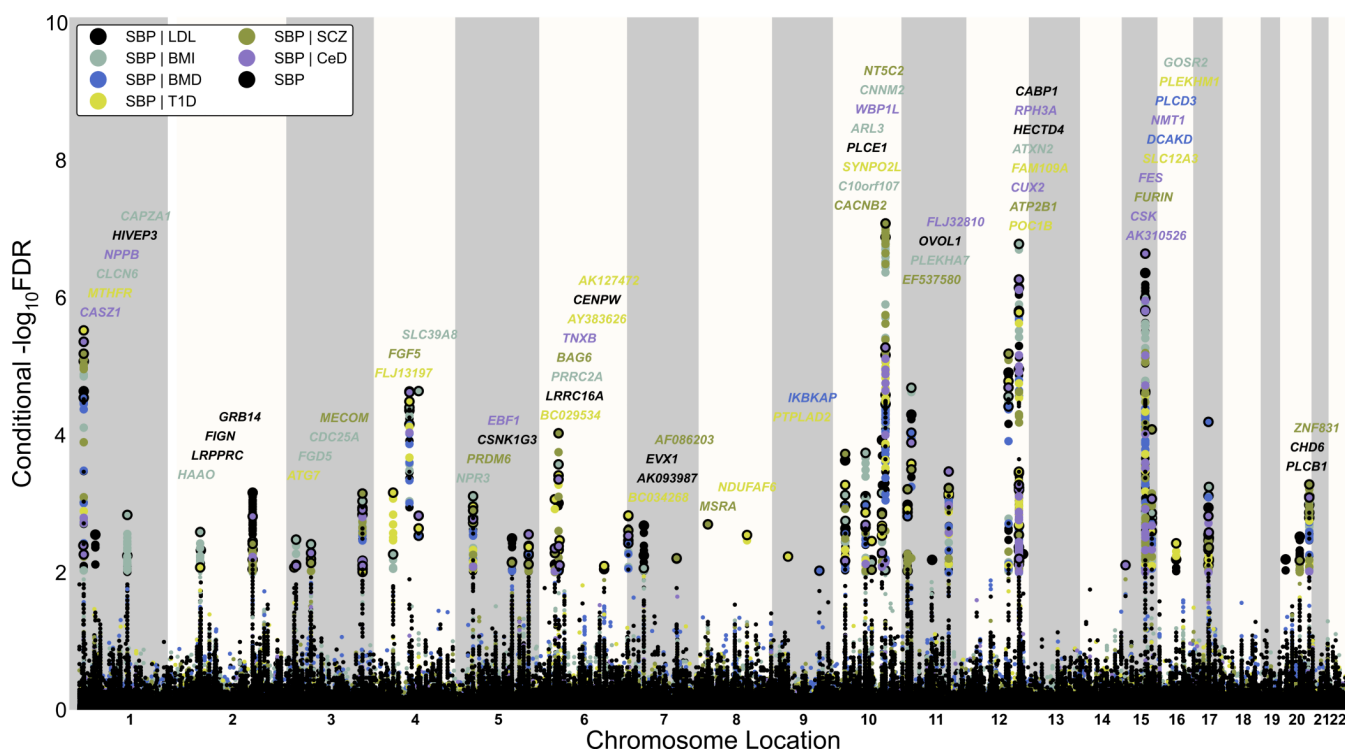


Figure 2. ‘Conditional FDR Manhattan plot’

‘Conditional FDR Manhattan plot’ of conditional $-\log_{10}(\text{FDR})$ values for Systolic Blood Pressure (SBP) alone (black) and SBP given the associated phenotypes low density lipoprotein cholesterol (LDL; SBP|LDL, red), body mass index (BMI; SBP|BMI, orange), bone mineral density (BMD; SBP|BMD, green), type 1 diabetes (T1D; SBP|T1D, purple), schizophrenia (SCZ; SBP|SCZ; turquoise) and celiac disease (CeD; SBP|CeD, blue). SNPs with conditional $-\log_{10} \text{FDR} > 2$ (i.e. $\text{FDR} < 0.01$) are shown with large points. A black circle around the large points indicates the most significant SNP in each LD block and this SNP was annotated with the closest gene which is listed above the symbols in each locus, except for the HLA region on chromosome 6, and in Table S2 (please see <http://hyper.ahajournals.org>). The figure shows the localization of 62 loci on 16 chromosomes (1-12, 15-17 and 20). Details for the loci with $-\log_{10} \text{FDR} > 2$ (i.e. $\text{FDR} < 0.01$) are shown in Table 1.

Table 1

The GWAS data used in the current study

Disease/Trait	N	# SNPs	Reference
Systolic Blood Pressure (SBP)	203,056	2,382,073	Ehret GB, Munroe PB, Rice KM, et al. Genetic variants in novel pathways influence blood pressure and cardiovascular disease risk. <i>Nature</i> 2011;478:103-9.
Low Density Lipoprotein (LDL)	99,900	2,508,375	Teslovich TM, Musunuru K, Smith AV, et al. Biological, clinical and population relevance of 95 loci for blood lipids. <i>Nature</i> 2010;466:707-13.
High Density Lipoprotein (HDL)	96,598	2,508,370	
Triglycerides (TG)	96,568	2,508,369	Lango Allen et al. Hundreds of variants clustered in genomic loci and biological pathways affect human height. <i>Nature</i> 2010, 467: 832-8
Height (HT)	183,727	2,398,527	
Body Mass Index (BMI)	123,865	2,400,377	Speliotes EK, Willer CJ, Berndt SI, et al. Association analyses of 249,796 individuals reveal 18 new loci associated with body mass index. <i>Nat Genet</i> 2010;42:937-48.
Waist to hip ratio (WHR)	77,167	2,376,820	Heid IM, Jackson AU, Randall JC, et al. Meta-analysis identifies 13 new loci associated with waist-hip ratio and reveals sexual dimorphism in the genetic basis of fat distribution. <i>Nat Genet</i> 2010;42:949-60.
Type 2 Diabetes (T2D)	22,044	2,426,886	Voight BF, Scott LJ, Steinthorsdottir V, et al. Twelve type 2 diabetes susceptibility loci identified through large-scale association analysis. <i>Nat Genet</i> 2010;42:579-89.
Type 1 Diabetes (T1D)	16,559	841,622	Barrett, J.C. et al. Genome-wide association study and meta-analysis find that over 40 loci affect risk of type 1 diabetes. <i>NatGen</i> 2009, 41, 703-7.
Rheumatoid arthritis (RA)	25,708	2,560,000	Stahl, E.A. et al. Genome-wide association study meta-analysis identifies seven new rheumatoid arthritis risk loci. <i>Nat Genet</i> 2010 42, 508-14.
Bone Mineral Density (BMD)	32,961	2,500,000	Estrada, K. et al. Genome-wide meta-analysis identifies 56 bone mineral density loci and reveals 14 loci associated with risk of fracture. <i>Nat Genet</i> 2012;44:491-501.
Celiac Disease (CeD)	15,283	528,969	Dubois, P.C. et al Multiple common variants for celiac disease influencing immune gene expression. <i>Nat Genet</i> 2010, 42, 295-302
Schizophrenia	21,856	1,171,056	Schizophrenia Psychiatric Genome-Wide Association Study (GWAS) Consortium. Genome-wide association study identifies five new schizophrenia loci. <i>Nat Genet</i> 2011;43:969-76.

For more details, see also <http://www.genome.gov/gwastudies>

Table 2

Independent loci associated with SBP through Conditional FDR (<0.01) with associated phenotypes.

Locus	SNP	Pos	Gene	chr	SBP p-value	SBP FDR	Min cond FDR	Associated Phenotype
1	rs2748975	1886519	<i>KIAA1751</i>	1	1.81E-06	0.01493	0.0095053	WHR
2	rs880315	10796866	<i>CASZ1</i>	1	1.44E-05	0.04983	0.0040514	CeD
3	rs17367504	11862778	<i>MTHFR</i> †	1	9.86E-11	0.00003	0.0000013	WHR
	rs2050265	11879699	<i>CLCN6</i>	1	2.38E-10	0.00003	0.0000026	WHR
4	rs6676300	11925300	<i>NPPB</i>	1	1.47E-05	0.04983	0.0054695	CeD
5	rs783622	42366988	<i>HIVEP3</i>	1	1.04E-05	0.03839	0.0028136	LDL
6	rs12048528	113210534	<i>CAPZA1</i>	1	3.84E-06	0.02209	0.0014541	BMI
	rs2932538	113216543	<i>MOV10</i> †	1	1.78E-06	0.01493	0.0014684	BMI
7	rs4332966	43083831	<i>HAAO</i>	2	1.58E-05	0.04983	0.0025790	BMI
8	rs9309112	44169889	<i>LRPPRC</i>	2	1.56E-05	0.04983	0.0047478	LDL
9	rs12619842	164945044	<i>FIGN</i>	2	1.01E-05	0.03839	0.0089999	LDL
	rs16849397	165108248	<i>GRB14</i>	2	4.76E-07	0.00665	0.0025354	WHR
10	rs2594992	11360997	<i>ATG7</i>	3	2.24E-06	0.01687	0.0076216	WHR
11	rs6806067	14948702	<i>FGD5</i>	3	2.23E-06	0.01493	0.0033240	BMI
12	rs6797587	48197614	<i>CDC25A</i>	3	1.32E-06	0.01180	0.0043919	BMI
13	rs223102	169100755	<i>MECOM</i> †	3	4.56E-08	0.00112	0.0006796	WHR
14	rs9290369	169324783	<i>MECOM</i>	3	8.04E-07	0.00909	0.0066551	WHR
15	rs10006384	38385187	<i>FLJ13197</i>	4	2.71E-06	0.01687	0.0054382	BMI
16	rs1458038	81164723	<i>FGF5</i> †	4	1.08E-09	0.00004	0.0000228	WHR
17	rs13107325	103188709	<i>SLC39A8</i> †	4	1.55E-07	0.00271	0.0000229	BMI
18	rs1173743	32775047	<i>NPR3</i>	5	4.78E-07	0.00665	0.0007773	BMI
	rs1173771	32815028	<i>C5orf23</i> †	5	8.44E-08	0.00162	0.0004338	WHR
19	rs458158	122482181	<i>PRDM6</i>	5	6.76E-06	0.02945	0.0071865	SCZ
20	rs11750782	122976743	<i>CSNK1G3</i>	5	6.75E-06	0.02945	0.0070289	BMD
21	rs11953630	157845402	<i>EBF1</i> †	5	3.64E-07	0.00558	0.0029954	WHR
22	rs199205	7736417	<i>BMP6</i>	6	2.29E-06	0.01687	0.0076216	WHR
23	rs9467445	25234884	<i>BC029534</i>	6	2.20E-06	0.01493	0.0011956	T1D
24	rs11754013	25370200	<i>LRRC16A</i>	6	1.32E-05	0.04368	0.0076472	LDL
25	rs2736155	31605199	<i>PRRC2A (BAT2)</i> †	6	1.41E-06	0.01180	0.0002670	BMI
	rs805303	31616366	<i>BAG6(BAT3)</i> †	6	8.17E-07	0.00909	0.0000941	SCZ
26	rs429150	32075563	<i>TNXB</i>	6	1.70E-05	0.04983	0.0090475	LDL
27	rs394199	33553580	<i>GGNBPI (AY383626)</i>	6	3.96E-05	0.08570	0.0034152	T1D
28	rs581484	126665180	<i>CENPW (C6orf173)</i>	6	3.08E-06	0.01922	0.0089438	LDL
29	rs853964	127029267	<i>AK127472</i>	6	2.63E-06	0.01687	0.0076216	WHR
30	rs2969070	2512545	<i>BC034268</i>	7	2.64E-07	0.00386	0.0014814	T1D
31	rs3735533	27245893	<i>HOTTIP (AK093987)</i>	7	1.37E-05	0.04368	0.0056631	LDL
32	rs7777128	27337113	<i>EVX1</i>	7	6.04E-06	0.02945	0.0020776	LDL
33	rs7787898	106409897	<i>AF086203</i>	7	2.60E-06	0.01687	0.0062017	SCZ

Locus	SNP	Pos	Gene	chr	SBP p-value	SBP FDR	Min cond FDR	Associated Phenotype
34	rs3088186	10226355	<i>MSRA</i>	8	1.97E-05	0.05707	0.0019924	SCZ
35	rs4735337	95973465	<i>NDUFA6 (C8orf38)</i>	8	3.54E-05	0.07505	0.0028564	T1D
36	rs12006112	21042299	<i>PTPLAD2</i>	9	5.02E-05	0.09719	0.0058735	T1D
37	rs4978374	111646983	<i>IKBKAP</i>	9	9.87E-06	0.03839	0.0094345	BMD
38	rs12570727	18425519	<i>CACNB2</i> †	10	4.07E-08	0.00093	0.0001882	SCZ
39	rs12258967	18727959	<i>CACNB2</i>	10	1.42E-07	0.00271	0.0015659	WHR
40	rs4590817	63467553	<i>C10orf107</i> †	10	3.40E-08	0.00077	0.0001588	WHR
41	rs12247028	75410052	<i>SYNPO2L</i>	10	1.59E-06	0.0132B	0.0067916	WHR
42	rs932764	95895940	<i>PLCE1</i> †	10	1.47E-07	0.00271	0.0001182	LDL
43	rs10786156	96014622	<i>PLCE1</i>	10	2.51E-06	0.01687	0.0020927	BMI
44	rs10883766	104464763	<i>ARL3</i>	10	1.91E-05	0.05707	0.0071447	CeD
	rs284844	126665180	<i>WBP1L (C10orf26)</i>	10	5.48E-09	0.00015	0.0000039	BMI
	rs1926032	127029267	<i>CNNM2</i>	10	2.77E-10	0.00003	0.0000001	BMI
	rs11191548	2512545	<i>NT5C2</i> †	10	2.43E-10	0.00003	0.0000001	SCZ
45	rs7129220	27245893	<i>EF537580</i> †	11	6.92E-08	0.00135	0.0006154	SCZ
46	rs1580005	27337113	<i>EF537580</i>	11	2.80E-06	0.01687	0.0057696	LDL
47	rs381815	106409897	<i>PLEKHA7</i> †	11	1.25E-09	0.00005	0.0000205	BMI
48	rs642803	10226355	<i>OVOL1</i>	11	1.14E-05	0.04368	0.0065527	LDL
49	rs633185	95973465	<i>FLJ32810</i> †	11	2.98E-08	0.00077	0.0004474	WHR
50	rs11105328	21042299	<i>POC1B (WDR51B)</i>	12	5.35E-10	0.00003	0.0000080	SCZ
	rs2681472	111646983	<i>ATP2B1</i> †	12	5.14E-13	0.00003	0.0000062	SCZ
51	rs7297186	1425519	<i>CUX2</i>	12	1.88E-06	0.01493	0.0005328	CeD
	rs3742004	18727959	<i>FAM109A</i>	12	6.39E-07	0.00783	0.0003417	WHR
	rs653178	63467553	<i>ATXN2</i>	12	4.58E-10	0.00003	0.0000002	BMI
	rs1005902	75410052	<i>HECTD4 (C12orf51)</i>	12	2.62E-06	0.01687	0.0005845	LDL
	rs12580178	95895940	<i>RPH3A</i>	12	4.21E-06	0.02209	0.0007345	LDL
52	rs7299238	96014622	<i>CABP1</i>	12	6.25E-05	0.10892	0.0053975	LDL
53	rs11070252	104464763	<i>GOLGA8T (AK310526)</i>	15	3.86E-06	0.02209	0.0078255	CeD
54	rs1378942	75077367	<i>CSK</i> †	15	1.63E-10	0.00003	0.0000002	CeD
55	rs8032315	91418297	<i>FURIN</i>	15	1.83E-07	0.00323	0.0000828	SCZ
	rs2521501	91437388	<i>FES</i> †	15	7.16E-08	0.00162	0.0011762	WHR
56	rs11643718	56933519	<i>SLC12A3</i>	16	3.30E-05	0.07505	0.0037698	T1D
57	rs4793172	43131480	<i>DCAKD</i>	17	7.05E-07	0.00783	0.0040625	SCZ
	rs2239923	43176804	<i>NMT1</i>	17	3.97E-07	0.00558	0.0008079	BMD
	rs12946454	43208121	<i>PLCD3</i>	17	5.17E-08	0.00112	0.0000647	BMD
58	rs11012		<i>PLEKHM1</i>	17	4.12E-05	0.08570	0.0034152	T1D
59	rs17608766		<i>GOSR2</i> †	17	4.59E-07	0.00665	0.0005684	BMI
60	rs6055905		<i>PLCB1</i>	20	3.04E-05	0.07505	0.0064506	LDL
61	rs6072403		<i>CHD6</i>	20	5.59E-06	0.02552	0.0058812	LDL
62	rs6015450		<i>ZNF831</i> †	20	5.63E-08	0.00135	0.0006154	SCZ

Independent complex or single gene loci ($r^2 < 0.2$) of SNP(s) with a conditional FDR (condFDR) < 0.01 in Systolic Blood Pressure (SBP) given the significance level in the associated phenotype. We defined the most significant SBP SNP in each LD block based on the minimum condFDR (min condFDR) for each associated phenotype. The most significant SNPs in each gene of the LD block are listed along with the associated phenotype that provided the signal. Low density lipoprotein (LDL) cholesterol, body mass index (BMI), waist hip ratio (WHR), bone mineral density (BMD), type 1 diabetes (T1D), celiac disease (CeD), schizophrenia (SCZ), chromosome location (Chr). SBP FDR values < 0.01 and p-values $< 5 \times 10^{-8}$ are in bold.

[†] Same locus identified in previous SBP genome-wide association studies. The most significant phenotype associations per gene are shown. All genes are shown in Table S1. All data were first corrected for genomic inflation. Gene titles and gene ontology functional terms are displayed in Table S2 (please see <http://hyper.ahajournals.org>). Ingenuity pathway analysis was used to generate a network displaying direct interactions among proteins encoded by these SBP-related genes (shown in Figure S3, please see <http://hyper.ahajournals.org>). The molecules associated with some of the top functional clusters of these genes are shown in Tables S3 and S4 (please see <http://hyper.ahajournals.org>).